ENCLOSURE # 3

BACKGROUND INFORMATION

Conference Plan: Justification

The subject of this Gordon Research Conference, "Proteolytic Enzymes and Their Inhibitors," is of fundamental interest to widely diversified groups of scientists ranging from chemists to medical researchers and pharmacologists.

To chemists, proteases can serve as excellent model enzymes and model proteins. Proteases were among the first enzymes to be crystallized and to have their amino acid sequence and three-dimensional structure determined. The catalytic mechanism of several proteases (chymotrypsin and carboxypeptidase, for example) is better understood at the atomic level than is that of any other enzyme. Functions of protease inhibitors are now also beginning to be appreciated in molecular detail. Thus, these enzymes and their inhibitors hold great fascination for basic biochemists and are frequently used as experimental systems for exploration of macromolecular structure.

At the same time (and largely because of the growing understanding of the basic structure and function of proteases and their inhibitors), these molecules are also of great interest to biomedical and clinical investigators including: a broad grouping of immunologists, hematologists, rheumatologists, and experimental pathologists interested in inflammation, connective tissue diseases, emphysema and cancer. This is because proteases and their regulatory endogenous inhibitors have been shown to play a central part in the homeostatic control of complement activation, of blood clotting and fibrinolysis, and of the generation of peptide-mediators of inflammation and blood pressure regulation (bradykinin, angiotensin I and II). Besides the established role of proteolytic cascades in immunological host defense (complement cascade) and diseases such as angioedema (complement and kinin cascades), hemophilia and other bleeding or clotting disorders (coagulation and fibrinolytic cascades), and hypertension (renin, angiotensin-converting enzyme, and kallikrein), proteases have also been implicated in fertility (acrosin in sperm penetration and plasminogen-activator in ovulation and embryo implantation). Proteases may also be important in cancer cell invasiveness and metastasis (again plasminogen-activator along, perhaps, with collogenase and cathepsin B).

These are but a few examples of the involvement of proteases and their inhibitors in fundamental biological processes and major human diseases. One could also cite evidence that an imbalance between leukocyte elastase and its chief regulator in lung tissue, alpha 1-proteinase inhibitor, constitutes the pathogenetic mechanism of destructive lung disease (pulmonary emphysema). Proteases are also instrumental in the post-translational processing (activation) of selected hormones [proinsulin, pro-opiomelanocortin (the common precursor of ACTH and beta-endorphin), vasopressin, oxytocin and somatostatin]. Similarly, proteases "process" macromolecular products of fibrocytes and smooth muscle cells (procollagen, for example).

All of the foregoing topics, from molecular structure and catalytic mechanism to role in protein-processing, are represented in the program of the 1984 Gordon Research Conference on Proteolytic Enzymes and Their Inhibitors. Leading experts in many of the fields mentioned above have been invited to present their newest findings and to lead the discussions. A list of speakers and a draft-program for the meeting will be found at the end of this proposal. Almost all of the listed speakers have already agreed to participate; the few who had not yet been heard from at the time this application was submitted are designated as tentative.

All conferees will also be urged to present posters, which will be kept in place through half the conference week (two poster sessions are planned). This approach was very successful at the 1982 Protease Conference where, all told, about 100 posters were displayed. In this way all participants, not just speakers, will have the feeling that they are true members of the Conference. Also, discussions among non-speakers can be facilitated by virtue of their scientific identification through their poster presentations. The individual themes of the program can be rounded-out by this additional forum for scientific exchange.

The 1984 Gordon Conference on Proteolytic Enzymes will be advertised in a March 1984 issue of The Journal Science (AAAS) as well as in the following specialty journals: Blood, American Review of Respiratory Disease, and The Journal of Immunulogy. We anticipate that conference attendance will exceed 100 registrants and will reflect a mix of academic, industrial and government scientists. Based on past experience at the 1980 and 1982 meetings (especially the latter where the present writer served as Vice-Chairman), a large number of applications will be received from the pharmaceutical industry, because of growing interest in the design and use of synthetic protease-inhibitors in the management of inflammation and hypertension. In 1982, there were a total of 160 scientists in attendance at this conference (145 in 1980). Of these, about 75% were from academic institutions, 20% from industry and the rest from governmental institutions or other groups.

The 1984 Gordon Conference on Proteolytic Enzymes will be the third such conference since the series began. Both previous meetings were unqualified successes, as judged by attendance, number of applications received (in 1984 as many applicants were turned away as were accepted) and responses of conferees to The Gordon Research Conference Evaluation Questionnaire (a sample copy is attached to this application). The Gordon Protease Conference is now recognized as one of the few, regular international forums for the exchange of knowledge in this area held in the United States. Previously, major meetings in the protease field tradionally took place in Europe.

Although proceedings of Gordon Research Conferences are never published (rules of the conference sponsors), it was the concensus of the vast majority of registrants in 1980 and 1982 (questionnaire analysis) that these meetings clarified problems and stimulated new ideas in protease chemistry and in development of new biomedical applications.

We hope it is clear from the above and from the specific details of the attached program that the field of science represented by this Conference is of considerable importance to human health, and that support for such a conference would be consonant with the goals and mission of The Council for Tobacco Research-U.S.A., Inc.